

**METHODS AND DEVICES FOR PROVIDING PROLONGED DRUG
THERAPY**

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. Application No. 09/070,666, filed April 30, 1998, which is a continuation of U.S. Application No. 08/910,593, filed July 31, 1997, which claims the benefit of U.S. Provisional Application Nos. 60/030,514 and 60/044,121, filed November 12, 1996 and April 22, 1997, respectively.

This application is also a continuation-in-part of U.S. Application No. 08/967,606, filed November 10, 1997, which claims the benefit of U.S. Provisional Application No. 60/031,741, filed November 25, 1996.

This application is also a continuation-in-part of U.S. Application No. 08/937,336, filed August 19, 1997.

BACKGROUND OF THE INVENTION

2. Field of the Invention

This invention pertains to methods and devices for maintaining a desired therapeutic drug effect over a prolonged therapy period. In particular, the invention is directed to methods and devices that provide drug release within the gastrointestinal tract at an ascending release rate over an extended time period. In this manner, drug is released at an ascending rate during a portion of the drug administration period sufficient to maintain a desired therapeutic drug effect throughout a prolonged therapy period.

**2. Description of the Related Art Including Information Disclosed Under
37 CFR 1.97 and 1.98**

To produce its pharmacological effects, a drug must be made available in appropriate concentrations at its site of action within the body. This availability is affected by numerous factors including the quantity of the drug administered, the extent and rate of its absorption from its administration site,

1 its distribution, binding or localization within tissues, its biotransformation and
2 its excretion. One commonly-used indicator of drug availability is the
3 concentration of drug that is obtained within the blood or plasma, or other
4 appropriate body fluid or tissue, of a patient following administration of the
5 drug. For convenience, this concentration may be referred to as "plasma
6 drug concentration" hereinafter which is intended to be inclusive of drug
7 concentration measured in any appropriate body fluid or tissue. Plasma drug
8 concentration measurements provide very useful information including, for
9 example, comparative information with regard to different drug dosage forms
10 and/or different drug administration routes. In addition, for many drugs,
11 various drug effects including both desired pharmacological effects, i.e.,
12 therapeutic drug effects, and undesired pharmacological effects, i.e., side
13 effects, have been correlated with specific plasma drug concentrations or
14 ranges of plasma drug concentrations.

15 For orally administered drug dosage forms, absorption occurs within
16 the gastrointestinal ("g.i.") tract and is affected by many factors including the
17 physicochemical properties of the local microenvironment, such as surface
18 area, blood flow and membrane characteristics (which vary significantly in the
19 different portions of the g.i. tract), the physicochemical properties of the drug
20 entity, drug concentration, the existence and activity of drug-specific transport
21 mechanisms, etc. One important factor in the rate of absorption of drug
22 administered as an oral dosage form is the rate at which drug is released
23 from the dosage form. Drug release rates for oral dosage forms are typically
24 measured as an *in vitro* rate of dissolution, i.e., a quantity of drug released
25 from the dosage form per unit time.

26 Conventional oral dosage forms can be described as "immediate-
27 release" because, generally, essentially the entire dose of drug is released
28 from the dosage form within a very short period, i.e., minutes, following
29 administration. As this bolus of released drug is absorbed, the plasma drug
30 concentration typically rapidly rises to a maximal or peak concentration and

1 subsequently declines as the drug is distributed, bound or localized within
2 tissues, biotransformed and/or excreted. The time period for this decline
3 varies for different drugs and depends on many factors but this time period
4 will be characteristic of a particular drug. Generally, during some portion of
5 the time period in which the plasma drug concentration rises, peaks and
6 declines, the drug provides its therapeutic effects, i.e., the plasma drug
7 concentration achieves or exceeds an effective concentration. Moreover, at
8 some point during this time period, the therapeutic effects disappear, i.e.,
9 when the plasma drug concentration declines to a level that is below an
10 effective concentration. In addition, often, during a portion of this time
11 surrounding the time the peak concentration is attained, i.e., when the plasma
12 drug concentration is in its highest range, undesired side effects may become
13 apparent.

14 In view of the above, it will be appreciated that continued drug
15 effectiveness occurs during the time period when the plasma drug
16 concentration is within the effective plasma drug concentration range.
17 Because the plasma drug concentration declines over time, however, multiple
18 doses of the immediate-release drug dosage form must be administered at
19 appropriate intervals to ensure that the plasma drug concentration remains in
20 or, again, rises to, the effective concentration range. At the same time,
21 however, there is a need to avoid or minimize plasma drug concentrations
22 that rise to, and/or that remain for too long within, the higher ranges where
23 side effects become apparent. Accordingly, for many drugs, multiple,
24 separate doses of the immediate-release dosage form must be administered
25 at appropriate intervals to maintain a satisfactory balance of desired and
26 undesired pharmacological effects over a prolonged therapy period.

27 One focus of efforts to improve drug therapy has been directed to
28 providing non-immediate-release oral drug dosage forms that affect
29 absorption of the drug primarily by altering the release rate of the drug from
30 the dosage form. Examples of such non-immediate-release delivery systems

1 include delayed-release and sustained-release systems. Sustained-release
2 dosage forms generally release drug for an extended time period compared
3 to an immediate-release dosage form. There are many approaches to
4 achieving sustained release of drugs from oral dosage forms known in the art.
5 These different approaches include, for example, diffusion systems such as
6 reservoir devices and matrix devices, dissolution systems such as
7 encapsulated dissolution systems (including, for example, "tiny time pills") and
8 matrix dissolution systems, combination diffusion/dissolution systems,
9 osmotic systems and ion-exchange resin systems as described in
10 *Remington's Pharmaceutical Sciences*, 1990 ed., pp. 1682-1685.

11 It is believed to be particularly desirable to provide sustained-release
12 oral dosage forms that provide drug release at a substantially constant
13 release rate over an extended time period. In this manner, for many drugs,
14 the plasma drug concentration initially ascends for a short period of time as
15 drug release begins and then remains substantially constant over an
16 extended time period as drug release continues at a constant rate. For many
17 drugs, this substantially constant plasma drug concentration correlates with
18 substantially constant drug effectiveness over a prolonged therapy period. In
19 addition, because an initial relatively high peak plasma drug concentration is
20 avoided, side effects may be less of a problem. Accordingly, advantages of
21 constant-release dosage forms include decreasing the number of doses of a
22 drug that need to be administered over time and providing a better balance of
23 desired and undesired pharmacological effects of the drug.

24 Osmotic dosage forms, in particular, have been notably successful at
25 providing constant-release of drugs over extended time periods. Osmotic
26 dosage forms, in general, utilize osmotic pressure to generate a driving force
27 for imbibing fluid into a compartment formed, at least in part, by a
28 semipermeable wall that permits free diffusion of fluid but not drug or osmotic
29 agent(s), if present. A substantially constant rate of drug release can be
30 achieved by designing the system to provide a relatively constant osmotic

1 pressure and having suitable exit means for the drug formulation to permit the
2 drug formulation to be released at a rate that corresponds to the rate of fluid
3 imbibed as a result of the relatively constant osmotic pressure. A significant
4 advantage to osmotic systems is that operation is pH-independent and thus
5 continues at the osmotically-determined rate throughout an extended time
6 period even as the dosage form transits the gastrointestinal tract and
7 encounters differing microenvironments having significantly different pH
8 values.

9 Surprisingly simple but highly effective osmotic devices comprising
10 drug in a mixture with excipients, optionally including osmotically active
11 component(s), within the compartment are known in the art. Although
12 effective for many drugs, the release rate in these devices often declines over
13 time and complete delivery of the drug load may not occur. A more
14 sophisticated type of osmotic device comprises two component layers within
15 the compartment formed by the semipermeable wall. One component layer
16 comprises drug in a mixture with excipients, optionally including osmotically
17 active component(s), that will form a deliverable drug formulation within the
18 compartment and the second component layer comprises osmotically active
19 component(s) but does not contain drug. The osmotically active
20 component(s) in the second component layer typically comprise
21 osmopolymer(s) having relatively large molecular weights and which exhibit
22 "swelling" as fluid is imbibed such that release of these components through
23 the drug formulation exit means does not occur. The second component
24 layer is referred to as a "push" layer since, as fluid is imbibed, the
25 osmopolymer(s) swell and push against the deliverable drug formulation of
26 the first component layer to thereby facilitate release of the drug formulation
27 at a substantially constant rate. The above-described devices are known, for
28 example, from the following US Patents, owned by Alza Corporation:
29 4,327,725; 4,612,008; 4,783,337; and 5,082,668, each of which is
30 incorporated in its entirety by reference herein.

1 Although constant-release dosage forms have proven effective for
2 many different drug therapies, there are clinical situations where these have
3 not been entirely satisfactory. It has been observed that for some patients
4 being treated with constant-release dosage forms for some conditions or
5 diseases, the therapeutic effectiveness of the drug decreases at time periods
6 before the end of the desired therapy period despite the maintenance of
7 substantially constant drug release that would be expected to provide
8 continued effectiveness. Accordingly, there remains a need to provide
9 methods and devices for maintaining a desired therapeutic drug effect over a
10 desired prolonged therapy period when sustained-release dosage forms that
11 release drug at a substantially constant rate over an extended time period are
12 not satisfactory.

13 14 BRIEF SUMMARY OF THE INVENTION

15 One aspect of the present invention pertains to providing improved
16 drug therapy for those clinical situations where therapeutic effectiveness of an
17 administered drug therapy unexpectedly decreases at time periods before the
18 end of the intended therapy period. It has been surprisingly discovered that,
19 in an exemplary clinical situation, administration of drug at a release rate that
20 is ascending, rather than substantially constant, over an extended time period
21 provided therapeutic efficacy that did not decrease before the end of the
22 prolonged therapy period.

23 With the discovery that administration of drug at a release rate that is
24 substantially ascending provides improved drug therapy, a need arises for
25 sustained-release oral dosage forms adapted to provide such a release rate
26 over a suitable extended time period. Accordingly, other aspects of the
27 present invention include providing oral sustained-release dosage forms that
28 provide an ascending drug release rate over an extended time period,
29 methods of making such dosage forms and methods of using such dosage

1 forms to maintain therapeutic effectiveness for a desired prolonged therapy
2 period.

3 It has been surprisingly discovered that oral osmotic dosage forms
4 exhibiting an ascending drug release rate for an extended time period can be
5 achieved. In particular, the present invention is directed to osmotic dosage
6 forms having bi-layer or tri-layer tablet cores that are adapted to provide
7 ascending drug release rates over an extended period. In addition, to provide
8 for an initial rapid onset of drug action, the present invention is also related to
9 dosage forms that additionally comprise a dose of drug for immediate release.

10 The bi-layer oral osmotic dosage forms of the present invention include
11 a first component layer, comprising a selected drug and excipients for forming
12 a deliverable drug composition when hydrated, and a second push layer,
13 comprising a fluid-expandable osmopolymer and excipients, contained within
14 a compartment formed by a semipermeable membrane and having exit
15 means for drug release from the compartment. The two layers are
16 compressed into bi-layer tablet cores before the semipermeable membrane is
17 applied and a suitable orifice for drug release therethrough is formed.
18 Importantly, the bi-layer tablet cores disclosed herein are formed when two
19 component layers are compressed together to provide a longitudinally
20 compressed tablet ("LCT") core having a "capsule-shaped" configuration with
21 a different layer at each narrow end.

22 The combination of features including the osmotic properties of the
23 component layers, the fluid flux properties of the semipermeable membrane
24 and the configuration of the tablet core ensures that drug is released at an
25 ascending rate over an extended time period. In a preferred embodiment,
26 sufficient activity in the push layer is achieved by use of a relatively large
27 concentration (at least about 35%) of osmotically effective solute, or
28 osmagent, such as sodium chloride. In addition, sorbitol is preferably
29 included in the first component layer.

1 The tri-layer oral osmotic dosage forms of the present invention include
2 a novel tri-layer tablet core surrounded by a semipermeable membrane and
3 having suitable exit means for releasing drug formulation through the
4 semipermeable membrane. The novel tri-layer tablet core has a first drug-
5 containing layer, a second drug-containing layer and a third push layer. In
6 operation, through the cooperation of the dosage form components, drug is
7 successively released from the first drug-containing layer and then from the
8 second drug-containing layer. It has been discovered that a drug
9 concentration gradient facilitates the achievement of an ascending drug
10 release rate for an extended time period. Consequently, the other excipients
11 in the drug-containing layers may be more flexibly varied and adjusted for
12 other purposes such as manufacturing convenience and pharmaceutical
13 elegance. In this manner, dosage forms that exhibit reliable drug release
14 having the desired sustained and ascending rate over an extended time
15 period can be reliably and efficiently manufactured.

16 It is preferred to use the LCT core configuration, as described above,
17 to enhance hydration of the tri-layer core. In addition, a flux-enhancing agent
18 is preferably included in the semipermeable wall composition. In a presently
19 preferred embodiment, the combination of features including the LCT tri-layer
20 core configuration, a suitable drug concentration gradient between the first
21 and second component layers, the osmotic properties of the component
22 layers and the fluid flux properties of the semipermeable membrane achieves
23 the desired ascending rate of drug release over an extended time period.

24 There are numerous clinical situations and drug therapies that could be
25 improved with the use of dosage forms that provide a sustained and
26 ascending release rate over an extended time period. Exemplary dosage
27 forms, as disclosed herein, comprise CNS-acting drugs and cardiovascular-
28 acting drugs. It will be appreciated by persons of skill in the art that the
29 invention is applicable to many other types of drugs and drug therapies.
30 Examples of suitable types of drugs include, but are not limited to, anti-

1 infectives, analgesics, anesthetics, antiarthritics, antiasthmatics,
2 anticonvulsants, antidepressants, antidiabetics, antidiarrheals, antihistamines,
3 antiinflammatories, antimigraines, antineoplastics, antiparkinsonisms,
4 antipruritics, antipsychotics, antipyretics, antispasmodics, anticholinergics,
5 sympathomimetics, calcium channel blockers, beta blockers, antiarrhythmics,
6 antihypertensives, ACE inhibitors, diuretics, vasodilators, decongestants,
7 hormones, hypnotics, immunosuppressives, parasymphomimetics,
8 prostaglandins, proteins, peptides, sedatives and tranquilizers.

9 The exemplary clinical situation described herein involves treatment of
10 ADHD with methylphenidate therapy. Accordingly, the present invention also
11 pertains to making oral methylphenidate sustained release dosage forms that
12 provide a sustained and ascending release rate of a drug over an extended
13 time period.

14 It has further been discovered that oral methylphenidate sustained
15 release dosage forms that provide an ascending release rate of a drug over
16 an extended time period can be used to provide effective once-a-day therapy
17 for ADHD. Thus, the present invention also pertains to improving drug
18 therapy for ADHD by eliminating the need for multiple daily doses of
19 methylphenidate yet providing therapeutic efficacy throughout the day that
20 compares to the therapeutic efficacy provided by multiple doses of immediate
21 release methylphenidate.

22 The above-described features and advantages, as well as others, will
23 become more apparent from the following detailed disclosure of the invention
24 and the accompanying claims.

25 Although the present invention is illustrated herein by exemplary
26 dosage forms containing specific exemplary drugs, methods of making such
27 dosage forms and methods of using methylphenidate-containing dosage
28 forms to provide a desired therapeutic outcome, the invention is not limited by
29 the exemplary embodiments. The invention broadly embraces oral sustained-
30 release dosage forms that provide an ascending drug release rate over an

1 extended time period, methods of making such dosage forms and methods of
2 using such dosage forms to maintain therapeutic effectiveness for a desired
3 prolonged therapy period with respect to any appropriate drugs and drug
4 therapies as would be apparent to a person of skill in the art in view of the
5 disclosure herein.

6 7 BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

8 Figure 1 is a cross-section view of a bi-layer osmotic dosage form in
9 accord with the present invention.

10 Figure 2 is a cross-section view of a tri-layer osmotic dosage form,
11 additionally comprising an immediate-release drug overcoat and an aesthetic
12 overcoat, in accord with the present invention.

13 Figure 3 is a graph illustrating the quantity of drug released over time
14 from a preferred embodiment of the present invention as described in Example
15 6.

16 Figure 4 is a graph illustrating the plasma drug concentration over time
17 obtained following administration of methylphenidate in accord with an
18 experimental regimen (open diamonds) and a standard regimen (closed circles)
19 as described in Example 7.

20 21 DETAILED DESCRIPTION OF THE INVENTION

22 Many effective drug therapies utilize immediate-release oral dosage
23 forms administered at spaced intervals to provide and maintain a desired
24 therapeutic effect over a prolonged therapy period. In addition, sustained-
25 release dosage forms for many drugs are known and, in particular, constant-
26 release oral dosage forms are known. There are many examples of effective
27 drug therapies that utilize constant-release oral dosage forms to provide a
28 desired therapeutic effect over a prolonged therapy period. In many cases,
29 these drug therapies offer advantages over drug therapies that utilize
30 immediate-release oral dosage forms administered at spaced intervals.

1 There are clinical situations, however, where the constant-release dosage
2 form has unexpectedly exhibited decreases in therapeutic effectiveness at
3 time periods before the end of the desired prolonged therapy period.

4 One example of a clinical situation where drug therapy with sustained-
5 release oral drug dosage forms that provide a substantially constant rate of
6 drug release for an extended period has not been entirely satisfactory is with
7 the use of central nervous system (CNS) stimulant drugs to treat various
8 conditions and disorders including Attention Deficit Disorder (ADD) and
9 Attention Deficit Hyperactivity Disorder (ADHD). These disorders are
10 commonly diagnosed in children but can also occur in adults. Treatment of
11 these and other psychological conditions with CNS stimulant drugs has a long
12 history. About 25 years ago, methylphenidate replaced amphetamine as the
13 primary stimulant prescribed to treat ADHD in children.

14 Methylphenidate therapy in children with ADHD has been extensively
15 studied and the efficacy and safety of this treatment is well-established.
16 Methylphenidate therapy has been shown to be very effective in reducing
17 symptoms of hyperactivity, inattention and impulsivity in children with ADHD.
18 The goal of drug therapy is to control the behavioral symptoms during the
19 daytime while the patient is in school or otherwise involved in activities where
20 symptom control benefits the patient's ability to learn and/or otherwise
21 beneficially participate in activities. Because of concerns related to side
22 effects, however, drug therapy is typically discontinued during at least a
23 portion of the evening and through the night in most patients. Depending on
24 the patient's particular circumstances, drug therapy may or may not be
25 discontinued over the weekends as well.

26 Treatment commonly utilizes immediate-release methylphenidate
27 administered two or three times during the day. For various reasons, patients
28 often experience difficulty complying with this administration schedule.
29 Because of abuse potential, methylphenidate is a controlled substance and
30 thus drug access is a special concern. This dosage regimen generally

1 requires that at least one dose is administered during the school day and, as
2 a rule, children are not permitted to self-administer the drug at school. For
3 this reason, authorized school personnel generally take on the responsibility
4 for administering the drug to children during the school day, however, this
5 approach raises issues of medical privacy and potential stigmatizing of the
6 child by peers. In addition, the compliance issue becomes further
7 complicated as transportation, storage and supply of the drug typically must
8 be documented and/or monitored and the schedules of the different parties
9 involved, i.e., the child, the educators and the authorized school personnel,
10 must be coordinated and accommodated. The unfortunate result is that
11 doses may be given late or missed altogether resulting in decreased efficacy
12 of the therapy.

13 For all of the above reasons, it would appear that a sustained-release
14 oral dosage form of methylphenidate that provided substantially constant drug
15 release over an extended period to thereby eliminate the need for dose
16 administration during the school day would be a welcome improvement. In
17 fact, such a sustained-release dosage form of methylphenidate has been
18 commercially available for several years. Clinical experience with this dosage
19 form, however, has been disappointing in that behavioral symptoms in
20 patients taking the controlled-release dosage form is less well-controlled later
21 in the day compared to those patients taking multiple doses of the immediate-
22 release dosage form. In addition, the slower onset of action of the controlled-
23 release dosage form compared to the immediate-release dosage form is
24 unsatisfactory for many patients.

25 It has been surprisingly discovered that administration of
26 methylphenidate at a release rate that is substantially ascending, rather than
27 substantially constant, over an extended time period provided therapeutic
28 efficacy similar to the efficacy obtained with multiple doses of immediate-
29 release methylphenidate dosage forms. Details of this discovery are
30 disclosed in copending U.S. Application No. 910,593, filed July 31, 1997, of

1 which the present application is a continuation-in-part application. To briefly
2 review, in one clinical study, a comparison of the behavioral, attentional, and
3 cognitive efficacy of placebo and methylphenidate administered according to
4 three different release rate regimens, i.e., immediate-release, constant-
5 release and ascending-release, was performed. The immediate-release
6 methylphenidate was administered as two spaced-apart doses. The
7 constant-release regimen was administered as an initial loading dose with the
8 remaining total quantity administered in equal small doses at closely-spaced
9 intervals extending past the time of administration of the second immediate-
10 release dose. The ascending-release regimen was administered as an initial
11 loading dose with the remaining total quantity administered in increasing
12 small doses at closely-spaced intervals extending past the time of
13 administration of the second immediate-release dose.

14 In this study, the constant-release regimen was observed to have
15 decreased clinical effectiveness compared to the immediate-release regimen
16 at evaluation periods following administration of the second immediate-
17 release dose. On the other hand, the ascending-release regimen
18 demonstrated comparable clinical efficacy to the immediate-release regimen
19 during these evaluation periods. Thus, the ascending-release regimen
20 avoided the decrease in therapeutic efficacy seen with the constant-release
21 regimen at later time periods during the prolonged therapy period.

22 While not making any assertions with respect to mechanism(s) of
23 action of the present invention, it is noted that the development of acute
24 tolerance to methylphenidate has been proposed as an explanation for the
25 unsatisfactory decrease in therapeutic effectiveness that has been observed
26 in some cases. Support for this theory was demonstrated in a second clinical
27 study wherein a decrease in effectiveness of methylphenidate was seen over
28 a prolonged therapy period both when a constant-release regimen was
29 utilized as well as when very closely-spaced doses of immediate-release
30 methylphenidate dosage forms were administered. An ascending-release

1 regimen, however, was shown to maintain therapeutic efficacy throughout the
2 prolonged therapy period.

3 With the discovery that drug effectiveness over a prolonged therapy
4 period may be improved in some circumstances with administration of drug in
5 an ascending release rate over an extended period, a need arises for
6 sustained-release oral dosage forms adapted to provide such a release rate.
7 In one aspect of the present invention, it has been surprisingly discovered
8 that bi-layer oral osmotic dosage forms can be adapted to meet this need. In
9 another aspect, it has been surprisingly discovered that sustained-release
10 oral osmotic dosage forms having novel tri-layer cores can be produced that
11 also achieve sustained release of drug formulations at an ascending rate for
12 an extended time period.

13 As is known in the prior art, osmotic dosage forms comprising
14 compressed tablet cores require a short time period following administration
15 in which to become hydrated sufficiently to begin releasing drug. For some
16 drug therapies, the slight delay in initial drug release is unsatisfactory. This
17 problem is overcome with the addition of an initial dose of drug supplied in an
18 immediate-release overcoat applied to the surface of the semipermeable
19 membrane. In preferred embodiments of the present invention, as disclosed
20 herein, such an immediate-release drug overcoat is applied onto the surface
21 of the bi-layer or tri-layer osmotic dosage forms.

22 For purposes of this disclosure, the following definitions shall apply:

23 For clarity and convenience herein, the convention is utilized of
24 designating the time of drug administration as zero hours ($t = 0$ hours) and
25 times following administration in appropriate time units, e.g., $t = 30$ minutes or
26 $t = 2$ hours, etc.

27 As used herein, the term "drug" generally refers to a pharmacologically
28 active substance that, when delivered into a living organism, produces a
29 desired, usually beneficial, effect. Drug compositions are generally utilized
30 clinically in the form of a pharmaceutically acceptable salt thereof. In

1 addition, some drug compositions exhibit chirality and, thus, have more than
2 one optical isomer. Because the different optical isomers may exhibit
3 different pharmacological effects, it may be advantageous to utilize a
4 substantially pure form of one optical isomer of a drug, or a pharmaceutically
5 acceptable salt thereof. Accordingly, the term "drug" refers to a clinically
6 useful form of a drug composition including a pharmaceutically acceptable
7 salt thereof and including a substantially pure isomer of the drug composition
8 and a pharmaceutically acceptable salt thereof. Although a limited number of
9 drugs are represented in the exemplary embodiments herein, the invention is
10 not to be limited by the exemplary embodiments but is fully applicable to other
11 suitable drugs as would be understood by persons of skill in the art.

12 The amount of drug incorporated in the dosage forms of the present
13 invention varies depending on the particular drug, the therapeutic indication
14 and the desired administration period, e.g., every 12 hours, every 24 hours,
15 etc. Depending on the dose of drug desired to be administered, one or more
16 of the dosage forms may be administered.

17 A drug "release rate" refers to the quantity of drug released from a
18 dosage form per unit time, e.g., milligrams of drug released per hour (mg/hr).
19 Drug release rates are calculated under *in vitro* dosage form dissolution
20 testing conditions known in the art. As used herein, a drug release rate
21 obtained at a specified time "following administration" refers to the *in vitro*
22 drug release rate obtained at the specified time following implementation of
23 an appropriate dissolution test. The dissolution test utilized in the Examples
24 described herein were performed on dosage forms placed in metal coil
25 sample holders attached to a USP Type VII bath indexer and immersed in
26 about 50 ml of acidified water (pH = 3) equilibrated in a constant temperature
27 water bath at 37°C. Aliquots of the release rate solutions were injected into a
28 chromatographic system to quantify the amounts of drug released during the
29 testing intervals.

1 A commonly-used reference measurement for evaluating drug release
2 from oral dosage forms is the time at which 90% of drug within a dosage form
3 has been released. This measurement is referred to as the " T_{90} " for the
4 dosage form.

5 An "immediate-release" dose of a drug refers to a dose that is
6 substantially completely released within a time period of about 1 hour or less
7 and, preferably, about 30 minutes or less. An immediate-release dose of
8 drug applied as a coating on the surface of a dosage form, as used herein,
9 refers to a dose of a drug prepared in a suitable pharmaceutically acceptable
10 carrier to form a coating solution that will dissolve rapidly upon administration
11 to thereby provide an immediate-release dose of drug. As is known in the art,
12 such immediate-release drug overcoats may contain the same or a different
13 drug or drugs as is contained within the underlying dosage form.

14 A "periodic release rate" refers to the quantity of drug released from a
15 dosage form during a specified periodic interval as determined at the end of
16 that specified periodic interval, i.e., at each periodic interval when a
17 determination is made, the quantity of drug released represents the periodic
18 release rate during that periodic interval. For example, the quantity of drug
19 released as determined at $t = 1$ h represents the periodic release rate from
20 the dosage form during the first hour following administration and the quantity
21 of drug released as determined at $t = 2$ h represents the periodic release rate
22 during the second hour following administration, etc.

23 An "ascending release rate" refers to a periodic release rate that is
24 increased over the immediately-preceding periodic release rate, where the
25 periodic intervals are the same. For example, when the quantity of drug
26 released from a dosage form is measured at hourly intervals and the quantity
27 of drug released during the fifth hour following administration (determined at t
28 $= 5$ hours) is greater than the quantity of drug released from the dosage form
29 during the fourth hour following administration (determined at $t = 4$ hours), an
30 ascending release rate from the fourth hour to the fifth hour has occurred.

1 It will be appreciated that the first periodic release rate measured, e.g.,
2 the periodic release rate at $t = 1$ hour (unless equal to 0), will always be
3 greater than the release rate during the preceding period, e.g., the hour
4 before the dosage form was administered, and, thus, the first periodic release
5 rate always constitutes an occurrence of an ascending release rate.

6 The ascending release rates described herein refer to the release rate
7 from a dosage form adapted to provide sustained release of drug and do not
8 include release of drug from any immediate-release drug coating that may be
9 applied to the dosage form. In dosage form embodiments additionally
10 comprising an immediate-release dose of a drug applied as a coating onto the
11 underlying dosage form, the drug release measured at $t = 1$ hour will
12 generally reflect both the drug released from the immediate-release drug
13 coating and any drug released from the underlying dosage form, however, the
14 quantity of drug released from the drug overcoat is disregarded in determining
15 whether the drug release rate at $t = 2$ hours is greater than the drug release
16 at $t = 1$ hour.

17 As used herein with reference to the time period during which an
18 ascending release rate is provided, "an extended time period" refers to a time
19 period beginning at $t = 0$ hours and continuing through at least the mid-point,
20 and preferably beyond the mid-point, of the relevant T_{90} of the dosage form.
21 Because the dosage forms of the present invention are intended to provide
22 sustained release of drug, a suitable T_{90} for purposes of this invention is at
23 least about 6 hours and, consequently, the "extended time period" during
24 which an ascending release rate is provided is at least 3 hours.

25 In accord with the above-recited definitions, an "ascending release rate
26 over an extended time period" refers to ascending release rates of drug
27 obtained from the time of administration of the dosage form through, and
28 preferably beyond, the mid-point of the relevant T_{90} for the dosage form. To
29 illustrate, consider a situation where a dosage form has a T_{90} of about 8
30 hours. In this situation, an "ascending release rate over an extended time

1 period" is achieved when the release rate at each hour through $t = 4$ hours is
2 greater than the release rate in the immediately-preceding hour. Preferably,
3 the release rate continues to ascend during time periods beyond $t = 4$ hours.

4 Bi-layer oral osmotic dosage forms and methods of making and using
5 such dosage forms are known in the art, for example, as described and
6 claimed in the following US Patents, owned by Alza Corporation: 4,327,725;
7 4,612,008; 4,783,337; and 5,082,668, each of which is incorporated in its
8 entirety by reference herein. The prior art bi-layer osmotic dosage forms
9 achieve sustained release of drug formulations wherein a relatively brief initial
10 period of ascending release rates is followed by substantially constant release
11 rates over a major portion of the T_{90} period. The achievement of an
12 ascending release rate for an extended time period of at least 50% of the T_{90}
13 period is not found within the prior art. The dosage forms of the present
14 invention are useful for providing continuous effective drug therapy over a
15 prolonged therapy period without exhibiting a decrease in effectiveness
16 during the latter portion of the prolonged therapy period.

17 The bi-layer oral osmotic dosage forms of the present invention include
18 a first component layer, comprising a selected drug and excipients for forming
19 a deliverable drug composition when hydrated, and a second push layer,
20 comprising a fluid-expandable osmopolymer and excipients, wherein the two
21 layers are compressed into bi-layer tablet cores before the semipermeable
22 membrane is applied and a suitable orifice for drug release therethrough is
23 formed. The combination of features including the osmotic properties of the
24 component layers, the fluid flux properties of the semipermeable membrane
25 and the configuration of the tablet core ensures that drug is released at an
26 ascending rate over an extended time period.

27 Importantly, the bi-layer tablet cores of the present invention are
28 configured such that each component layer is substantially round in cross-
29 dimension with a circumferential width and a length between a top and a
30 bottom end. The two layers are compressed together longitudinally such that

1 the resulting bi-layer tablet core has the same circumferential width as the
2 component layers and a length that combines the lengths of the component
3 layers. The overall configuration can be described as “capsule-shaped”
4 wherein the bi-layer tablet core has a circumferential width that is less than its
5 length and has a rounded “narrow” top end and a rounded “narrow” bottom
6 end and wherein each narrow end comprises a different component tablet
7 layer.

8 For purposes of this disclosure, the above-described tablet cores are
9 referred to as longitudinally compressed tablet (“LCT”) cores. This LCT
10 configuration ensures that, as the push layer expands longitudinally within the
11 compartment formed by the semipermeable membrane, the surface area of
12 the push layer in contact with the semipermeable membrane is increased
13 more than when other configurations are used.

14 In a preferred embodiment, sufficient activity in the push layer is
15 achieved by use of a relatively large concentration (at least about 35%) of
16 osmotically effective solute, or osmagent, such as sodium chloride.
17 Consequently, the size of the push layer is relatively large and may be slightly
18 larger than the first component layer containing the drug and excipients. In
19 addition, for certain embodiments, sorbitol was found to be a useful excipient
20 in the first component layer. It has been surprisingly discovered that the
21 combination of features described above, including the LCT core
22 configuration, the relatively high percent of osmagent and, in some exemplary
23 embodiments, the use of sorbitol as an excipient provides the desired
24 ascending release rate over an extended time period from bi-layer oral
25 osmotic dosage forms. Exemplary embodiments of such bi-layer osmotic
26 dosage forms are detailed below in Examples 1 - 3.

27 An embodiment of a bi-layer oral osmotic dosage form 15 is shown in
28 cross-section in Figure 1. The components are not drawn to scale. The bi-
29 layer LCT core comprises a first component layer 21, containing drug and
30 selected excipients, and a second push layer 29, containing at least one fluid-

1 expandable osmopolymer and optionally containing at least one osmagent
2 along with selected excipients. Suitable excipients are known in the art and
3 include diluents, carriers, binders, fillers and processing aids. A
4 semipermeable membrane 57 surrounds the bi-layer tablet core to form a
5 compartment and a suitably sized orifice 55 is formed through the
6 semipermeable membrane and into the first component layer 21 to permit
7 drug formulation to be released from within the compartment. As illustrated,
8 the orifice 55 is preferably formed in the narrow end of the dosage form
9 comprising the first component layer. In operation, through cooperation of the
10 bi-layer osmotic dosage form components, drug is released from the first
11 drug-containing layer at an ascending release rate for an extended time
12 period. Although not shown in Figure 1, an immediate-release dose of a drug
13 may be provided by applying a drug-containing overcoat to a bi-layer dosage
14 form, if desired, as described elsewhere herein.

15 In addition to the above-described bi-layer osmotic dosage forms, it
16 has been surprisingly discovered that oral osmotic dosage forms exhibiting an
17 ascending drug release rate for an extended time period can also be
18 achieved with a novel tri-layer tablet core surrounded by a semipermeable
19 membrane and having suitable exit means for releasing drug formulation
20 through the semipermeable membrane. The novel tri-layer tablet core has a
21 first drug-containing layer, a second drug-containing layer and a third push
22 layer. In operation, through the cooperation of the dosage form components,
23 drug is successively released, in a sustained and controlled manner, from the
24 first drug-containing layer and then from the second drug-containing layer
25 such that an ascending release rate over an extended time period is
26 achieved.

27 It has been discovered that a drug concentration gradient between the
28 first and second drug-containing layers of the tri-layer core facilitates the
29 achievement of an ascending drug release rate for an extended time period
30 from the tri-layer osmotic dosage form. Consequently, the other excipients in

1 the drug-containing layers may be more flexibly varied and adjusted for other
2 purposes such as manufacturing convenience and pharmaceutical elegance.
3 For example, the tri-layer osmotic dosage forms preferably avoid the use of
4 sorbitol as an excipient. This provides manufacturing efficiency and product
5 shelf-life advantages since sorbitol is very hygroscopic and attracts moisture
6 during storage which can pose difficulties in handling and manufacturing as
7 well as longer-term stability concerns. In addition, sufficient activity in the
8 push layer may be achieved with the use of a relatively lower concentration
9 (less than about 25%) of osmotically effective solute such that the size of the
10 push layer can be smaller relative to the size of the two drug-containing
11 layers. Preferably, the push layer is smaller than the combined size of the
12 first and second drug-containing layers. An advantage to a smaller-sized
13 push layer is that larger doses of drug, if desired, can be accommodated
14 without the overall size of the dosage form becoming so large as to engender
15 manufacturing challenges and/or to become unpalatable to patients.

16 In a presently preferred embodiment, the hydration rate of the tri-layer
17 osmotic dosage form is improved with the inclusion of a flux-enhancing agent
18 in the semipermeable membrane. In addition, it is preferred to use the
19 longitudinally compressed tablet ("LCT") core configuration, as described
20 above, for the tri-layer osmotic dosage forms to also enhance hydration. In a
21 presently preferred embodiment, the combination of features including the
22 LCT tri-layer core configuration, a suitable drug concentration gradient
23 between the first and second component layers, the osmotic properties of the
24 component layers and the fluid flux properties of the semipermeable
25 membrane achieves the desired ascending rate of drug release over an
26 extended time period. Advantageously, such preferred embodiments exhibit
27 consistent and reliable operation and can be efficiently manufactured on a
28 large-scale basis.

29 A preferred embodiment of a tri-layer oral osmotic dosage form
30 additionally comprising an immediate-release dose of drug applied as an

1 overcoat and an aesthetic overcoat 14 is shown in cross-section in Figure 2.
2 The tri-layer LCT core comprises a first component layer 20, containing a
3 selected drug in a pharmaceutically acceptable form along with selected
4 excipients; a second component layer 18, containing a higher concentration
5 of drug along with selected excipients; and a third push layer 28, containing at
6 least one osmopolymer and optionally containing at least one osmagent along
7 with selected excipients. A semipermeable membrane 56 surrounds the tri-
8 layer tablet core to form a compartment and a suitably sized orifice 54 is
9 formed through the semipermeable membrane and into the first component
10 layer to permit drug formulation to be released from within the compartment.
11 As illustrated, the orifice 54 is preferably formed in the narrow end of the
12 dosage form comprising the first component layer. In operation, through
13 cooperation of the tri-layer osmotic dosage form components, drug is
14 successively released, in a sustained and controlled manner, from the first
15 drug-containing layer and then from the second drug-containing layer at an
16 ascending release rate for an extended time period.

17 As shown in Figure 2, the preferred embodiment further comprises an
18 immediate-release dose of drug contained within an overcoat 60 applied onto
19 the surface of the tri-layer osmotic dosage form. The drug is mixed with
20 suitable excipients such as, for example, hydroxypropylmethylcellulose, to
21 prepare a solution for coating onto the surface of the semipermeable
22 membrane of the tri-layer osmotic dosage form that will rapidly dissolve and
23 release drug following administration.

24 As shown in Figure 2, it is also preferred to provide an optional
25 aesthetic overcoat 62 applied onto the surface of the drug-containing
26 overcoat 60. As known in the art, such aesthetic overcoats provide
27 advantages including taste-masking, improved appearance and "glidability"
28 for facilitating swallowing and further processing steps such as printing,
29 packaging, etc. Exemplary embodiments of tri-layer osmotic dosage forms

1 that exhibit a substantially ascending release rate over an extended time
2 period are detailed below in Examples 4 – 6 and Examples 8 and 9.

3 The continued maintenance of therapeutic effectiveness over a
4 prolonged therapy period by the administration of the oral osmotic dosage
5 forms that exhibit an ascending release rate over an extended time period of
6 the present invention has been demonstrated. An exemplification is
7 described below in Example 7. In particular, it has been discovered that such
8 osmotic dosage forms containing methylphenidate can be used to provide
9 effective once-a-day therapy for ADHD. This discovery represents an
10 important improvement in drug therapy for ADHD by eliminating the need for
11 multiple daily doses of methylphenidate yet providing therapeutic efficacy
12 throughout the day that compares to the therapeutic efficacy provided by
13 multiple doses of immediate release methylphenidate.

14 The following examples are illustrative of the present invention, and the
15 examples should not be considered as limiting the scope of the invention in
16 any way, as these examples, and other equivalents thereof, will become
17 apparent to those versed in the art in the light of the present disclosure and
18 the accompanying claims.

19

20 Example 1

21 Bi-layer oral osmotic dosage forms were made in accord with
22 conventional manufacturing processes known in the art and disclosed in
23 detail in copending U.S. Application No. 967,606, filed November 10, 1997, of
24 which the present application is a continuation-in-part application. Briefly, a
25 first component layer, containing methylphenidate hydrochloride and selected
26 excipients, and a second push layer, containing suitable osmopolymers, 40%
27 by weight of an osmagent and selected excipients, were separately prepared
28 by granulation methods. Next, the first component layer and the second push
29 layer granulation preparations were longitudinally compressed together to
30 form bi-layer LCT cores. A selected semipermeable membrane was then

1 coated around the bi-layer LCT cores and a suitable 30 mil orifice for drug
2 release was formed therethrough and into the first component layer.

3 Each dosage form as prepared comprised:

4

5 First component layer

6

7	14.08 mg	methylphenidate hydrochloride
8	90.26 mg	poly(ethylene)oxide (200,000 number-average
9		molecular weight)
10	5.5 mg	poly(vinylpyrrolidone) (40,000 number-average
11		molecular weight)
12	0.11 mg	magnesium stearate
13	0.555 mg	butylated hydroxy toluene

14

15 Second push layer

16

17	71.032 mg	poly(ethylene)oxide (7,000,000 number-average
18		molecular weight)
19	52.8 mg	sodium chloride
20	6.6 mg	poly(vinylpyrrolidone) (40,000 number-average
21		molecular weight)
22	1.32 mg	red ferric oxide
23	0.132 mg	magnesium stearate
24	0.555 mg	butylated hydroxy toluene

25

26 Semipermeable Membrane

27

28	15.3 mg	cellulose acetate (39.8% acetyl content)
29	1.7 mg	poly(ethylene glycol) (3350 number-average
30		molecular weight)

31

1 The periodic release rates from the dosage form were determined
2 hourly for ten hours using *in vitro* dissolution testing. A residual quantity of
3 drug of 0.72 mg remained in the dosage form. The results are shown in
4 Table 1 along with an indication of whether an ascending release rate
5 occurred.

6

Table 1		
Time (hours)	Quantity of drug released (mg)	Ascending Release Rate Occurrence
1	0.22	YES
2	1.45	YES
3	1.72	YES
4	1.84	YES
5	2.05	YES
6	2.21	YES
7	2.13	NO
8	1.26	NO
9	0.39	NO
10	0.09	NO

7
8 As seen from Table 1, drug was released from the dosage forms at an
9 ascending rate for an extended time period, i.e., more than 90% of the drug
10 was released by $t = 8$ hours and ascending release rates occurred through $t =$
11 6 hours, an extended period of time well beyond the mid-point of the T_{90} .

12
13 Example 2

14 Bi-layer oral osmotic dosage forms were made in accord with
15 conventional manufacturing processes known in the art and disclosed in
16 detail in copending U.S. Application No. 967,606, filed November 10, 1997, of
17 which the present application is a continuation-in-part application. Briefly, a

1 first component layer, containing methylphenidate hydrochloride, sorbitol and
2 selected excipients, and a second push layer, containing suitable
3 osmopolymers, 40% by weight of an osmagent and selected excipients, were
4 separately prepared by granulation methods. Next, the first component layer
5 and the second push layer granulation preparations were longitudinally
6 compressed together to form bi-layer LCT cores. A selected semipermeable
7 membrane was then coated around the bi-layer LCT cores and a suitable 30
8 mil orifice for drug release was formed therethrough.

9 Each dosage form as prepared comprised:

10

11 First component layer (110 mg)

12		
13	12.8%	methylphenidate hydrochloride
14	54.75%	poly(ethylene)oxide (200,000 number-average
15		molecular weight)
16	25.4%	sorbitol
17	5%	hydroxypropylmethylcellulose (11,200 number-
18		average molecular weight)
19	2%	magnesium stearate
20	0.05%	butylated hydroxy toluene

21

22 Second push layer (132 mg)

23		
24	53.85%	poly(ethylene)oxide (7,000,000 number-average
25		molecular weight)
26	40%	sodium chloride
27	5%	hydroxypropylmethylcellulose (11,200 number-
28		average molecular weight)
29	1%	red ferric oxide
30	0.1%	magnesium stearate
31	0.05%	butylated hydroxy toluene

Semipermeable Membrane (42 mg)

47.5% cellulose acetate (39.8% acetyl content)
47.5% cellulose acetate (32% acetyl content)
5% poly(ethylene glycol) (3350 number-average
molecular weight

The periodic release rates from the dosage form were determined hourly for twelve hours. No residual quantity of drug remained in the dosage form. The results are shown in Table 2 along with an indication of the occurrences of an ascending release rate.

Table 2		
Time (hours)	Quantity of drug released (mg)	Ascending Release Rate Occurrence
1	0.13	YES
2	1.16	YES
3	1.53	YES
4	1.61	YES
5	1.75	YES
6	1.79	YES
7	2.13	YES
8	2.18	YES
9	1.07	NO
10	0.43	NO
11	0.17	NO
12	0.13	NO

1 As seen from Table 2, more than 90% of the drug was released by t =
2 9 hours and ascending release rates occurred through t = 8 hours, an
3 extended time period well beyond the mid-point of the T₉₀.

4 5 Example 3

6 Bi-layer oral osmotic dosage forms additionally comprising an
7 immediate-release dose of drug applied as an overcoat onto the
8 semipermeable membrane were made in accord with conventional
9 manufacturing processes known in the art and disclosed in detail in
10 copending U.S. Application No. 967,606, filed November 10, 1997, of which
11 the present application is a continuation-in-part application. Briefly, a first
12 component layer, containing methylphenidate hydrochloride, sorbitol and
13 selected excipients, and a second push layer, containing suitable
14 osmopolymers, 39.8% by weight of an osmagent and selected excipients,
15 were separately prepared by granulation methods. Next, the first component
16 layer and the second push layer granulation preparations were longitudinally
17 compressed together to form bi-layer LCT cores. A selected semipermeable
18 membrane was then coated around the bi-layer LCT cores and a suitable 30
19 mil orifice for drug release was formed therethrough. A drug-containing
20 overcoat mixture was prepared and coated onto the semipermeable
21 membrane of the osmotic dosage form. Optionally, a taste-masking overcoat
22 is also applied.

23 Each osmotic bi-layer dosage form as prepared comprised:

24 25 First component layer

26		
27	14 mg	methylphenidate hydrochloride
28	61 mg	poly(ethylene)oxide (2,000,000 number-average
29		molecular weight)
30	27.5 mg	sorbitol

1	5.5 mg	polyvinylpyrrolidone
2	2.2 mg	magnesium stearate
3	0.055 mg	butylated hydroxy toluene
4		
5		<u>Second push layer</u>
6		
7	72 mg	poly(ethylene)oxide (7,000,000 number-average
8		molecular weight)
9	53 mg	sodium chloride
10	6.6 mg	polyvinylpyrrolidone
11	1.3 mg	red ferric oxide
12	0.132 mg	magnesium stearate
13	0.066 mg	butylated hydroxy toluene

14

15 Semipermeable Membrane

16		
17	20 mg	cellulose acetate (39.8% acetyl content)
18	20 mg	cellulose acetate (32% acetyl content)
19	2 mg	poly(ethylene glycol) (4000 number-average
20		molecular weight)

21

22 An immediate-release drug-containing overcoat comprising 60%

23 hydroxypropylmethylcellulose and 40% methylphenidate hydrochloride is

24 prepared and a final solution of 10 mg (i.e., containing 4 mg of

25 methylphenidate salt) is coated onto the semipermeable membrane of the

26 osmotic dosage form.

27 The periodic release rates from the drug overcoat and the osmotic

28 dosage form were determined at 30 minutes, 1 hour and then hourly for the

29 next nine hours. The 4 mg of methylphenidate contained within the drug

30 overcoat was released within the first 30 minutes and the periodic release

31 rate shown at $t = 1$ hour of 0.41 mg constitutes drug released from the bi-

1 layer osmotic dosage form during the second 30-minute interval. No residual
2 quantity of drug remained in the dosage form. The hourly results are shown
3 in Table 3 along with an indication of the occurrences of an ascending release
4 rate.

5

Table 3		
Time (hours)	Quantity of drug released (mg)	Ascending Release Rate Occurrence
1	0.41	YES
2	1.05	YES
3	1.49	YES
4	1.57	YES
5	1.71	YES
6	1.75	YES
7	2.09	YES
8	2.14	YES
9	1.32	NO
10	0.48	NO

6
7 As seen from Table 3, exclusive of the immediate-release drug
8 overcoat, more than 90% of the drug was released by t = 9 hours and
9 ascending release rates occurred through t = 8 hours, an extended period of
10 time well beyond the mid-point of the T_{90} .

11 Example 4

12 Tri-layer oral osmotic dosage forms were made in accord with
13 conventional manufacturing processes known in the art and disclosed in
14 detail in copending U.S. Application No. 937,336, filed August 19, 1997, of
15 which the present application is a continuation-in-part application. Briefly, a
16 first component layer, containing pseudoephedrine hydrochloride and
17

1 selected excipients, a second component layer, containing a higher
 2 concentration of pseudoephedrine hydrochloride and selected excipients, and
 3 a third push layer, containing suitable osmopolymers, an osmagent and
 4 selected excipients, were separately prepared by granulation methods. Next,
 5 the first component layer, second component layer and the third push layer
 6 granulation preparations were longitudinally compressed together to form tri-
 7 layer LCT cores. A selected semipermeable membrane was then coated
 8 around the tri-layer LCT cores and a suitable 30 mil orifice for drug release
 9 was formed therethrough.

10 Each dosage form as prepared comprised:

11

12 First component layer

13

14	4.4 mg	pseudoephedrine hydrochloride
15	15.3 mg	poly(ethylene)oxide (300,000 number-average
16		molecular weight)
17	1.1 mg	hydroxypropylmethylcellulose (9,200 number-
18		average molecular weight)
19	1.1 mg	polyoxyethylene 40 stearate
20	0.11 mg	magnesium stearate

21

22 Second component layer

23

24	13.5 mg	pseudoephedrine hydrochloride
25	2.59 mg	poly(ethylene)oxide (300,000 number-average
26		molecular weight)
27	0.9 mg	hydroxypropylmethylcellulose (9,200 number-
28		average molecular weight)
29	0.9 mg	polyoxyethylene 40 stearate
30	0.018 mg	red ferric oxide
31	0.09 mg	magnesium stearate

Third push layer

1		
2		
3	22.2 mg	poly(ethylene)oxide (7,000,000 number-average
4		molecular weight)
5	12 mg	sodium chloride
6	2 mg	hydroxypropylmethylcellulose (9,200 number-
7		average molecular weight)
8	2 mg	polyoxyethylene 40 stearate
9	1.2 mg	cross-linked acrylic acid polymer
10	0.4 mg	red ferric oxide
11	0.2 mg	magnesium stearate

Semipermeable Membrane

12		
13		
14		
15	11.4 mg	cellulose acetate (39.8% acetyl content)
16	0.6 mg	polyethylene glycol (3350 average number
17		molecular weight)

18

19 The periodic release rates from the osmotic dosage form were

20 determined hourly for 7 hours and results are shown in Table 4 along with an

21 indication of the occurrences of an ascending release rate.

Table 4		
Time (hours)	Quantity of drug released (mg)	Ascending Release Rate Occurrence
1	0.13	YES
2	0.65	YES
3	2.2	YES
4	2.78	YES
5	3.24	YES
6	3.14	YES
7	3.43	YES

As seen from Table 4, about 87% of drug was released during the first 7 hours and ascending release rates were achieved throughout this period.

Example 5

Tri-layer oral osmotic dosage forms having a drug concentration gradient wherein the drug concentration was greater in the second component layer than the first component layer and also having viscosity gradients wherein the viscosity of the first component layer was less than the viscosity of the second component layer and the viscosity of the second component layer was lower than the viscosity of the third push layer were made in accord with conventional manufacturing processes known in the art and disclosed in detail in copending U.S. Application No. 937,336, filed August 19, 1997, of which the present application is a continuation-in-part application.

Each dosage form as prepared comprised:

1 First component layer (350 mg)

2

3 8.6% nicardipine

4 54.8% sorbitol

5 36.8% poly(ethylene)oxide (200,000 number-average
6 molecular weight)

7

8 Second component layer (120 mg)

9

10 45% nicardipine

11 50% poly(ethylene)oxide (300,000 number-average
12 molecular weight)

13 5% hydroxypropylmethylcellulose (9,200 number-
14 average molecular weight)

15

16 Third push layer (350 mg)

17

18 68.75% poly(ethylene)oxide (7,000,000 number-average
19 molecular weight)

20 20% sodium chloride

21 5% hydroxypropylmethylcellulose (9,200 number-
22 average molecular weight)

23 5% cross-linked acrylic acid polymer

24 1% ferric oxide

25 0.25% magnesium stearate

26

27 Semipermeable Membrane (43.5 mg)

28

29 95% cellulose acetate (39.8% acetyl content)

30 5% polyethylene glycol (3350 average number
31 molecular weight)

1 The dosage forms had 25 mil exit orifices formed through the
2 semipermeable membrane to permit release of drug formulation from within
3 the compartment. An ascending release rate for an extended time period of
4 about 16 hours was achieved with the dosage forms of Example 5.

6 Example 6

7 Preferred embodiments of the tri-layer osmotic dosage forms of the
8 present invention additionally comprising an immediate-release dose of drug
9 applied as an overcoat, as shown in Figure 2, were prepared in accord with
10 conventional osmotic tablet manufacturing processes.

11 The first component layer contained the following (by weight percent):
12 9.40% methylphenidate hydrochloride, 83.71% polyethylene oxide (Polyox N-
13 80 brand product of Union Carbide, Danbury, CT), 5% polyvinylpyrrolidone
14 (Kolidon 29-32 product of BASF Corp., Mt. Olive, NJ); 1.34% succinic acid;
15 0.5% stearic acid; and 0.05% butylated hydroxy toluene.

16 The second component layer contained the following (by weight
17 percent): 13.65% methylphenidate hydrochloride, 78.80% polyethylene oxide
18 (Polyox N-80 brand product of Union Carbide, Danbury, CT), 5%
19 polyvinylpyrrolidone (Kolidon 29-32 product of BASF Corp., Mt. Olive, NJ);
20 1.95% succinic acid; 0.5% stearic acid; 0.05% butylated hydroxy toluene; and
21 0.05% yellow ferric oxide, as coloring agent.

22 The third push layer contained the following (by weight percent): 73.7%
23 high molecular weight polyethylene oxide (Polyox 303 brand product of Union
24 Carbide, Danbury, CT), 20% sodium chloride; 5% polyvinylpyrrolidone
25 (Kolidon 29-32 brand product of BASF Corp., Mt. Olive, NJ); 0.25% stearic
26 acid; 0.05% butylated hydroxy toluene; and 1% green ferric oxide, as coloring
27 agent.

28 Each of the first component layer, second component layer and third
29 push layer were separately prepared into granulated compositions in a fluid
30 bed granulator. The granulated compositions were then compressed

1 sequentially and longitudinally on a rotary tablet press to produce the tri-layer
2 LCT cores. For each dosage form, 40 mg of the first component layer
3 granulation and 75 mg of the second component layer granulation were first
4 sequentially filled and tamped at 100 newtons into the die. Then, 90 mg of
5 the third push layer granulation to the die was added to the die and the final
6 compression was performed at 1500 newtons.

7 The composition of the semipermeable membrane was 83% by weight
8 cellulose acetate (CA 398-10, having an acetyl content of 39.8%, product of
9 Eastman Chemical, Kingsport, TN) and 17% by weight copolymer of ethylene
10 and propylene oxide (Poloxamer 188 brand product of BASF Corp., Mt. Olive,
11 NJ, added as a flux-enhancer. The two ingredients were dissolved in a blend
12 of 99.5% acetone and 0.5% water to form a 5% solids solution. In a pan
13 coater, the solution was then sprayed onto the tri-layer LCT cores to a weight
14 of 25.7 mg and a thickness of 4-5 mil.

15 After the semipermeable membrane had been applied to form a
16 compartment containing the tri-layer LCT cores, a 0.76 mm (40 mil) orifice
17 was drilled through the semipermeable membrane at the narrow end of the
18 compartment proximate to the first component layer to thereby form the
19 preferred tri-layer osmotic dosage forms, each containing 14 mg of
20 methylphenidate. Each dosage form was approximately 12 mm long with an
21 approximate diameter of 5.3 mm.

22 The drug overcoat for providing an immediate-release initial dose of
23 drug contains approximately 30% by weight methylphenidate hydrochloride,
24 approximately 70% by weight hydroxypropylmethylcellulose (Methocel E3
25 brand name product of Dow Chemical Co., Midland, MI), and a trace amount
26 of phosphoric acid (i.e., 20 ml of phosphoric acid added to 87 kg of drug in
27 solution). An aqueous coating solution is prepared by dissolving and mixing
28 the ingredients in water to form a solution with a 10% solids composition. In a
29 pan coater, the solution was then sprayed onto the semipermeable

1 membranes of the tri-layer osmotic dosage forms to a weight of about 14.0
2 mg comprising an immediate-release dose of methylphenidate of about 4mg.

3 The final aesthetic overcoat composition weighed 16.9 mg and
4 contained an underlayer of Opadry II, yellow (brand name product of
5 Colorcon, West Point, PA and an overlayer of Opadry, clear, with a trace
6 amount of carnauba wax, a glidant, prepared and applied as follows: first,
7 Opadry II (10%) is suspended in water (90%) and sprayed onto the drug-
8 overcoated dosage forms; next, clear Opadry (5%) is suspended in water
9 (95%) and sprayed onto the drug- and Opadry II-overcoated dosage forms;
10 finally, the dosage forms are tumbled in the coater with the carnauba wax for
11 ten minutes to allow about 100 ppm of wax to be uniformly distributed onto
12 the clear Opadry overcoat.

13 Many pharmaceutical dosage forms utilize drug in salt form such as the
14 hydrochloride salt of methylphenidate utilized herein. Such salt forms of
15 drugs prepared in aqueous solution, however, are prone to degradation and,
16 thus, often have stability and shelf-life problems. It has been discovered that
17 the addition of an appropriate pH-adjusting agent to the aqueous solution
18 decreases undesired degradation and improves the stability of the product. In
19 particular, in preferred embodiments tri-layer osmotic dosage forms
20 comprising methylphenidate hydrochloride, it has been discovered that
21 degradation of the drug ingredient can be minimized by the addition of
22 suitable antidegradation agents, i.e., succinic acid in the first and second
23 component layers and phosphoric acid in the drug overcoat. Other suitable
24 antidegradation agents include compounds that dissolve in an aqueous
25 medium are pharmaceutically acceptable, i.e., nontoxic and suitable for oral
26 administration to humans, and that exhibit sufficient pH-adjusting ability, i.e.,
27 have a pH no greater than 4 and preferably of 3 or below. Additional
28 examples include potassium phosphate, sodium phosphate, fumaric acid,
29 citric acid, tartaric acid, malic acid, hydrochloric acid, aspartic acid, glutamic
30 acid, oxalic acid, lactic acid, malonic acid, glyceric acid and ascorbic acid.

1 Periodic release rates for twenty-four sample dosage forms prepared
2 as described were determined hourly for 12 hours and are presented in graph
3 form in Figure 3. The mean quantities released each hour are shown in Table
4 5 along with an indication of the occurrences of an ascending release rate. It
5 is noted that the entire 4 mg immediate-release dose was essentially released
6 within the first hour and this quantity is disregarded with respect to the
7 determination that an ascending release rate occurred at $t = 2$ hours, i.e., the
8 mean quantity at $t = 2$ hours was compared to the mean quantity at $t = 1$
9 hours less 4 mg representing the immediate-release dose.

10

Table 5		
Time (hours)	Quantity of drug released (mg)	Ascending Release Rate Occurrence
1	4.098	YES
2	1.138	YES
3	1.650	YES
4	1.993	YES
5	2.043	YES
6	2.099	YES
7	1.966	NO
8	1.763	NO
9	0.428	NO
10	0.174	NO
11	0.084	NO
12	0.061	NO

11

12 As seen from Table 5, exclusive of the immediate-release drug
13 overcoat, more than 90% of the drug was released by $t = 8$ hours and
14 ascending release rates occurred through $t = 6$ hours, an extended period of
15 time well beyond the mid-point of the T_{90} .

Example 7

Therapeutic effectiveness of single doses of tri-layer osmotic dosage forms containing 14 mg of methylphenidate and additionally comprising an immediate-release drug overcoat containing 4 mg of methylphenidate was studied and compared to multiple doses of immediate-release methylphenidate.

Safety and therapeutic efficacy parameters were evaluated for a 12-hour period in the same subjects treated with the following regimens on different days: the experimental regimen wherein the tri-layer osmotic dosage form was administered once at $t = 0$ hours and the standard regimen wherein immediate-release methylphenidate (Ritalin®) was administered three times, at $t = 0$ hours, $t = 4$ hours, and $t = 8$ hours. Because the subjects were current methylphenidate users, the doses of methylphenidate administered during each regimen varied somewhat to match as closely as possible the "usual dose" each subject was routinely administered. For comparative purposes, the actual doses were normalized to a single 18 mg dose of the tri-layer osmotic dosage and to 15 mg of Ritalin® administered as three 5 mg doses.

Plasma drug concentrations were determined in all subjects at the same times during the study periods for each regimen. The selected times corresponded to the time just prior to, and 1.5 hours and 2.5 hours following, administration of the first two doses of immediate-release methylphenidate (i.e., at $t = 0$ hours, $t = 1.5$ hours, $t = 2.5$ hours, $t = 4$ hours, $t = 5.5$ hours, $t = 6.5$ hours), and just prior to, and 1.5 hours and 3.5 hours following, administration of the third dose (i.e., at $t = 8$ hours, $t = 9.5$ hours and $t = 11.5$ hours).

In Figure 4, plasma drug concentrations obtained from one group of study participants ($n = 16$) while treated with the experimental regimen (represented by open diamonds) and while treated with the standard regimen (represented by closed circles) are shown in graph form. A comparison of Figures 3 and 4 demonstrates a correlation between the *in vitro* release rates

1 through about $t = 8$ hours and the *in vivo* plasma drug concentrations through
2 about $t = 9.5$ hours.

3 As shown in Figure 4, the plasma drug concentration following each
4 administration of an immediate-release dose rises relatively rapidly and then
5 declines at a generally characteristic rate until the next dose is administered.
6 The plasma drug concentration following administration of the tri-layer
7 osmotic dosage form also exhibits an initial relatively rapid rise due largely to
8 release of drug from the immediate-release drug overcoat. Subsequently,
9 however, the plasma drug concentration does not decline but continues to
10 substantially ascend (save for a slight "dip" between $t = 5.5$ hours and $t = 6.5$
11 hours) through a time period of 9.5 hours. Particularly striking is the
12 difference during the time periods within about 1 hour before and about 1.5
13 hours following administration of the second and the third immediate-release
14 dose. With the standard regimen, during these periods, the plasma drug
15 concentration declines to a trough concentration and then rises again to a
16 peak concentration. With the experimental regimen, during these same time
17 periods, the plasma drug concentration is substantially smoothly ascending
18 and exhibits no peaks and troughs.

19 Safety and therapeutic parameters, including behavioral, attentional
20 and cognitive functions, were assessed hourly during the first three hours and
21 the last three hours of the study period and at two-hour intervals in between.
22 The clinical effectiveness of the experimental regimen was closely
23 comparable to the clinical effectiveness of the standard regimen throughout
24 the twelve-hour study period. An effective once-a-day therapy for ADHD
25 provides many advantages and offers a significant improvement in drug
26 therapy by eliminating the need for multiple daily doses of methylphenidate
27 while providing continued therapeutic efficacy throughout the day.

28
29
30

Example 8

Tri-layer oral osmotic dosage forms were made in accord with the manufacturing processes of Example 6 but comprising twice as much methylphenidate, i.e., a total of 28 mg of methylphenidate contained within the first and second component layers and 8 mg of methylphenidate in the drug overcoat. All of the remaining ingredients are also doubled so that the weight percents are the same as in Example 6. The third push layer is also doubled. The semipermeable membrane had the same composition as in Example 6 but was applied to a weight of about 34 mg.

These dosage forms exhibit release of 36 mg of methylphenidate with about 8 mg released immediately and the remaining 28 mg released at an ascending release rate over an extended time period.

Example 9

Tri-layer oral osmotic dosage forms were made in accord with the manufacturing processes of Example 6 but comprising a total of 42 mg of methylphenidate contained within the first and second component layers and 12 mg of methylphenidate in the drug overcoat. The first component layer contained the following (by weight percent): 11.5% methylphenidate hydrochloride, 81.6% polyethylene oxide (Polyox N-80 brand product of Union Carbide, Danbury, CT), 5% polyvinylpyrrolidone (Kolidon 29-32 product of BASF Corp., Mt. Olive, NJ); 1.3% succinic acid; 0.5% stearic acid; 0.05% butylated hydroxy toluene; and 0.05% yellow ferric oxide, as coloring agent. The second component layer contained the following (by weight percent): 19.8% methylphenidate hydrochloride, 72.7% polyethylene oxide (Polyox N-80 brand product of Union Carbide, Danbury, CT), 5% polyvinylpyrrolidone (Kolidon 29-32 product of BASF Corp., Mt. Olive, NJ); 1.95% succinic acid; 0.5% stearic acid; and 0.05% butylated hydroxy toluene. The third push layer is doubled from Example 6 and the semipermeable membrane had the same composition as in Example 6 but was applied to a weight of about 34 mg.

1 These dosage forms exhibit release of 54 mg of methylphenidate with
2 about 12 mg released immediately and the remaining 42 mg released at an
3 ascending release rate over an extended time period.

4 While there has been described and pointed out features and
5 advantages of the invention, as applied to present embodiments, those skilled
6 in the art will appreciate that various modifications, changes, additions, and
7 omissions in the descriptions within the specification can be made without
8 departing from the spirit of the invention.